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Effect of mesenchymal stromal cells for articular cartilage degeneration treatment: a meta-analysis

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Abstract

Background aims. Articular cartilage is an avascular tissue that has limited capacity for self-repair. Mesenchymal stromal cells have been considered as potential candidates for cartilage regeneration. However, clinical results of cartilage formation with the use of these cells need evaluation. We aimed to assess the effect of mesenchymal stromal cell treatment on articular cartilage defects. *Methods.* We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials with key words including "cartilage," "clinical trial," "mesenchymal," "stromal" and "stem cell" up to December 3, 2014. We selected the controlled trial that used treatment with mesenchymal stromal cells on cartilage injury compared with other treatment. We assessed the results of the meta-analysis by means of the error matrix approach. The outcome measures were ranked as comprehensive evaluation index, highest relevance; unilateral evaluation index, medial relevance; and single evaluation index, lowest relevance. *Results.* Eleven trials assessing 558 patients were included in the meta-analysis. Stem cell treatment significantly improved the American Orthopedic Foot and Ankle Society Scale (Standard Mean Difference, SMD, 0.91; 95% confidence interval [CI], 0.52 to 1.29). The Osteo-Arthritis Outcome Score was also significantly improved in stem cell treatment (SMD, 2.81; 95% CI, 2.02 to 3.60). Other comprehensive evaluation indexes, such as the American Knee Society Knee Score System (SMD −0.12, 95% CI, −1.02 to 0.78), the Hospital for Special Surgery Knee Rating Scale (SMD, 0.24, 95% CI, −0.56 to 1.05) and the International Knee Documentation Committee (SMD, −0.21; 95% CI, −0.77 to 0.34), appeared to have no significant differences by use of stem cell and other treatments. Overall, there was no obvious advantage regarding the application of stem cells to treat cartilage injury, compared with other treatments. *Conclusions.* In conclusion, assessment of the comprehensive evaluation index indicated that there were no significant differences after stem cell treatment. However, assessment of clinical symptoms and cartilage morphology showed significant improvement after stem cell treatment.

Key Words: *articular cartilage, clinical trial, mesenchymal stromal cell transplantation, meta-analysis*

Introduction

Articular cartilage provides a protective layer covering the joint surface; it acts to reduce the friction and weight-bearing of the bone joint [1]. Acute cartilage lesion is generally caused by a severe intra-articular fracture, whereas chronic cartilage defect is often a result of continuous osteoarthritis [2]. Various cartilage injuries often result in pain and swelling and frequently develop into degenerative lesion and chronic osteoarthritis. Instead of joint replacement and arthrodesis, the desired treatment of cartilage especially in younger population is preserving the joint function and cartilage regeneration [3].

Articular cartilage is an avascular tissue made of chondrocytes encapsulated in matrix of proteoglycans and collagens, which has only limited capacity for self-repair [4]. If the lesions are untreated, the fibrous tissue will cover the underlying bone, which could not provide enough mechanical and functional support. Therefore, spontaneous recovery is usually no improvement of the person's symptoms in the long term.

Cartilage injuries are usually treated through one of the three major types of surgery: marrow-stimulating techniques, mosaic plasty and cell-based therapies [5]. The marrow-stimulating techniques, such as drilling and micro-fracture, show a significant improvement in joint function and pain but are less than optimal for long-term outcomes [1]. Autologous chondrocyte implantation and matrix-associated autologous chondrocyte transplantation have been used in clinics for many

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years and have been proven for clinical trials by the US Food and Drug Administration (FDA) [4]. Difficulties related to the harvest and isolation of autologous chondrocytes restricted the clinical application. Mesenchymal stromal cells have been considered as a potential alternative in *in vitro* and preclinical studies. Allogeneic mesenchymal stromal cells isolated from umbilical cord blood have been approved by the Korean FDA for the treatment of osteoarthritis. However, the process of cartilage formation with the use of these cells is still in its infancy, and clinical results need further evaluation.

Previous studies have conducted a systematic review of the cell therapy, but evidence is insufficient [1,6]. We then collected data from the case-control study and conducted an update of systematic reviews to assess the treatment effect of mesenchymal stromal cell for the cartilage defect.

Methods

Data sources and searches

We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials with key words including "cartilage," "clinical trial," "mesenchymal," "stromal" and "stem cell." We did not apply any language restrictions and included all relevant articles up to December 3, 2014. Only parallel control trials were included. We also searched the reference list of identified trials.

Data selection

Authors SX and HL identified eligible reports; discrepancies were resolved through discussion. Eligibility criteria included the following requirements: (i) controlled trial; (ii) use of two comparator groups in which one group received mesenchymal stromal cells or other stem cells, except for chondrocytes, and the other group received treatment without stem cells.

Data analysis

We assessed the results of our meta-analysis by means of the error matrix approach. The error matrix approach has been validated in systematic reviews of cholecystectomy and inguinal hernia repair [7,8].

We assessed all the trials for the risk of bias (measured by the level of evidence), the risk of random error and the design error, as described previously [9].

We measured the risk of systematic error by use of the Cochrane Collaboration instrument for bias risk assessment [10]. The following components assessed the risk of bias: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; other bias. The risk of bias graph was also provided. Because masking the surgeon to allocation is difficult, the trials were therefore deemed to have a low risk of bias for the patients and assessors. Additionally, the level of evidence of each trial was also considered to assess the systematic error.

The systematic error was defined as follows: 1a is a meta-analysis of a low-bias, risk-randomized controlled trial and/or level 1 of evidence; 1b is a low-bias, risk-randomized controlled trial and/or level 1 of evidence; 1c is a meta-analysis of all randomized, controlled trials and/or level 1 to level 2 of evidence; 1d is a high-bias, risk-randomized, controlled trial and/or level 2 of evidence; 2a is a cohort study with concurrent controls without randomization; 2b is a cohort study with controls in the past without randomization; 3a is a case-control study; 3b is a retrospective study; 4 is a before-after study (without control group); 5 is a case report and case series.

The risk of random error is the risk of drawing a false conclusion that is based on sparse data. As the algorithms suggested by the Cochrane collaboration, standard error less than 0.20 is low risk for random error, 0.20 to 1.00 is moderate risk and greater than 1.00 is high risk. Studies with a high risk for random error were abandoned or considered irrelevant for decision-making.

The design error was measured by classifying the clinically relevant outcome according to the Grading of Recommendations Assessment, Development and Evaluation approach [11]. Publication bias was assessed by means of funnel plots. Results most important for clinical decision-making are the highest bars in the upper-left part of the plot.

Statistical analysis

We used the inverse variance method to pool continuous data and the Mantel-Haenszel method for dichotomous data (relative risk, RR); results are presented as standardized mean difference with 95% confidence intervals (CIs). We assessed statistical heterogeneity with the use of I^2. In the absence of statistical heterogeneity ($<50\%$), we used a fixed-effect model; otherwise we used a random-effects model. All tests were two-tailed, and a value of $P < 0.05$ was deemed statistically significant. We analyzed data with the use of Review Manager (Version 5.3) and STATA (version 12.0).